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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,762	10/12/2001	Margaret Shipp	DFN-031US	2130

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EXAMINER	
WINKLER, ULRIKE	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 11/03/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,762	SHIPP ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 3 .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,2,4-10,20 and 25-31 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,2,4-10,20 and 25-31 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 21 October 2001 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Amendment filed August 20, 2003 (Paper No. 13) in response to the Office Action of May 20, 2003 is acknowledged and has been entered. Claims 3, 11-19 and 21-24 have been cancelled and claims 25-31 have been added. Claims 1, 2, 4-10, 20 and 25-31 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Specification

The Office acknowledges the correction to the specification.

Sequence listing

Applicant's CRF and paper sequence listing have been entered.

Drawings

The drawings were objected to in the prior Office action as indicated in PTO-948 (paper No. 12), correction is required (27 CFR 1.121(d)) in reply to the instant Office action and corrections can no longer be held in abeyance.

Claim Rejections - 35 USC § 112

The rejection of claims 1-10, 20 and newly added claims 25-31 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide

comprising SEQ ID NO. 2 encoded by the nucleic acid sequence set forth in SEQ ID NO: 1 or 3, does not reasonably provide enablement for an isolated polypeptide or an isolated nucleic acid molecule that is at least 90% of 95% homologues to SEQ ID NO: 1, 2 or 3 **is maintained** for reasons of record.

Applicant's arguments have been fully considered but are not deemed persuasive. Applicant's arguments are that procedures for making variants of a nucleic acid sequence are conventional in the art especially when coupled to a catalytic activity. In this instance Applicant's arguments are that the new limitation "wherein elevated levels of said nucleic acid molecules are indicative of a malignancy", is the same as claiming a catalytic function.

The claims are now drawn to an isolated polynucleotide encoding a polypeptide of SEQ ID NO: 2 or an isolated polynucleotide which is at least 90% or 95% homologous to the amino acid sequence in of SEQ ID NO:2. This includes a whole universe of polypeptides with 90 or 95% identity to SEQ ID NO.2. The claims are drawn to an isolated nucleic acid comprising SEQ ID NO: 1, 3 or a polynucleotide encoding SEQ ID NO: 2 and complement thereof, it is not clear if the complement thereof is a full-length complement or if this includes smaller fragments.

According to the specification the term "isolated nucleic acid" encompasses insertion deletion or substitution (see page 20, lines 14-31), isolated nucleic acids include fragments of 15 nucleotides in length (page 19, lines 1-5) and nucleic acids includes naturally occurring allelic variants (page 18, lines 24-30). The specification does not provide a specific and measurable biological function or activity that can be correlated with the nucleic acid molecule Bal. Therefore, one cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to any polynucleotide fragment, which encodes a

polypeptide fragment with 90%-95% sequence homology to SEQ ID NO: 2 without any repeatable measurable activity that can be associated with the homologue. The newly added limitation "wherein elevated levels of said nucleic acid molecule are indicative of a malignancy" does not correct this lack of correlation between structure and function. The specification has only provided a comparison Bal in large B-cell lymphoma (DLB-Cl), where the increase of Bal in the DLB-Cl cell was compared to the control molecule Able. The specification has not provided any indication that an increase in Bal can be correlated all malignancies arising from any tissue in the body. The specification only provided the indication that a high level of Bal in a lymphoma correlates with a high risk indicating that treatment for these patients will not result in a favorable outcome. There is no indication in the specification that a molecule which is 90% homologous to SEQ ID NO:2 will be associated with the high risk lymphoma group.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al., Journal of Cell Bio. 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the

disclosed sequence can be tolerated that will allow the protein to function as a claimed "indicator of a malignancy". Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use any and all nucleic acid fragments with sequence similarity to the amino acid sequence shown in SEQ ID NO. 2. Therefore, in view of the speculative nature of the invention, the lack of predictability of the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed, which include variation in the nucleic acid sequence resulting in changes in the encoded protein sequence.

Note: the rejection of claims 1, 2, 25, 26, 27 and 28 can be overcome by indicating that "the complement thereof" is a "full-length complement".

The rejection of claims 1-10, 20 and newly added claims 25-31 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention **is maintained** for reasons of record. The written description in this case only sets forth SEQ ID NO: 1, 2 and 3 and therefore the written description is not commensurate in scope with claims that read on 90%-95 % sequence homology to SEQ ID NO. 2.

Applicant's arguments have been fully considered but are not deemed persuasive. Applicant's have deleted the reference to "allelic variants", applicant's arguments are that procedures for making variants of a nucleic acid sequence are conventional in the art especially

when coupled to a catalytic activity. In this instance applicants argue that the new limitation "wherein elevated levels of said nucleic acid molecules are indicative of a malignancy" is a sufficient catalytic activity that allows the ordinary artisan to predictably make the contemplated variants.

The claims are now drawn to an isolated polynucleotide encoding a polypeptide of SEQ ID NO: 2 or an isolated polynucleotide which is at least 90% or 95% homologous to the amino acid sequence in of SEQ ID NO:2. This includes a whole universe of polypeptides with 90% or 95% identity to SEQ ID NO.2. The claims are drawn to an isolated nucleic acid comprising SEQ ID NO: 1, 3 or a polynucleotide encoding SEQ ID NO: 2 and "complement thereof", it is not clear if the complement thereof is a full-length complement or if this includes smaller fragments.

According to the specification "isolated nucleic acid" encompasses insertions, deletions or substitutions (see page 20, lines 14-31), isolated nucleic acid molecules include fragments of 15 nucleotides in length (page 19, lines 1-5) and nucleic acids includes naturally occurring allelic variants (page 18, lines 24-30). No disclosure, beyond the mere mention of biologically active fragments is made in the specification. With the exception of nucleic acids encoding SEQ ID NO:2, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and/or encoded variants and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The amino acid sequence itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) the court held that a generic statement, which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". In this instance the specification has shown that an increase in the nucleic acid level of Bal is associated with high level risk in patients with diffuse large B-cell lymphoma (DLB-Cl). The specification has not provided any correlation between the level of Bal expression and any malignancy arising from any tissue in the body. The specification has shown that Bal is primarily expressed in lymphoid tissue. Furthermore, the limitation "wherein elevated levels of said nucleic acid molecules are indicative of a malignancy" does not provide predictable/repeatable means of measuring a structure function relationship. Therefore, only a nucleic acid sequence of SEQ ID No: 1 or 3 encoding the polypeptide sequence of SEQ ID NO. 2 meets the written description provision of 35 USC 112, first paragraph.

Note: the rejection of claims 1, 2, 25, 26, 27 and 28 can be overcome by indicating that "the complement thereof" is a "full-length complement".

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

ULRIKE WINKLER, PHD.
PATENT EXAMINER 10/31/03